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ON 28 October 2003

Christina M. Doyle

Applicant : Dalemans, et al.
Appl. No. : 09/581,976
Filed : June 20, 2000
Title : Compositions Comprising Human Papilloma Virus Proteins
and Fusion Proteins Adjuvanted with a CpG Oligonucleotide
Grp./A.U. : 1648
Examiner : B. Li

Docket No. : B45124

Assistant Commissioner of Patents
Box AF
Washington, D.C. 20231

DECLARATION OF DR. CATHERINE GÉRARD

1. I, Dr. Catherine Gérard, a citizen of Belgium and residing at 36, Kastanjeboslaan, 1640 Sint Genesius Rhode Belgium, Belgium, declares the following with respect to the invention described and claimed in the patent application 09/581976.

2. I have received the following academic qualifications:

- Bachelor's degree in biology in 1983, Free University of Brussels, Belgium;
- Ph. D. in biological sciences in 1989, Free University of Brussels, Belgium.

I am an employee of GSK Biologicals. I joined SmithKline Beecham Biologicals (the predecessor of GSK Biologicals) in 1996, as a Scientist in the R&D Department. I have been working on several cancer vaccine projects, including HPV-induced lesions and tumors; I am currently research Senior Scientist heading the preclinical tumor immunology group. I am an inventor of the above case.

3. I have read and am familiar with the Office Action dated August 28, 2001, and with the prior art cited in the Office Action. The prior art does not suggest the need for an improvement of HPV antigenicity.

4. At the time of filing the patent application, it was established that the E6 and E7 genes from HPV 16 were potential antigens to target HPV 16-induced lesions or tumors by immunotherapy (Proc. Natl. Acad. Sci. USA. 1991 January 1; 88 (1): 110–114 Human Papillomavirus Type 16 Nucleoprotein E7 is a Tumor Rejection Antigen by L Chen, EK Thomas, S Hu, I Hellstrom, and KE Hellstrom). It was also known that these antigens can serve as tumor rejection antigens. CTL raised against E6 or E7 from HPV16 can in certain circumstances have a therapeutic potential on E7 expressing murine tumors. Nothing was known however about whether E6 and E7 proteins of HPV18 could exert similar effects.

5. Furthermore, the best way to induce CTL against these antigens was not known. The publication published in 1997 by Boursnell et al. Vaccine 1996 14: 1485-1494 : Construction and characterisation of a recombinant vaccinia virus expressing human papillomavirus proteins for immunotherapy of cervical cancer. Boursnell ME, Rutherford E, Hickling JK, Rollinson EA, Munro AJ, Rolley N, McLean CS, Borysiewicz LK, Vousden K, Inglis SC. describes one way to achieve the induction of CTL against E7 proteins using a recombinant vaccinia virus. They describe the generation of the recombinant vaccinia virus coding for mutated, less oncogenic forms of the E6 and E7 antigens. Despite the fact that this recombinant vaccinia virus is shown to induce CTL at least against E7 of HPV16 (there is no demonstration that this is achieved by HPV18-derived proteins), however, the role or functionality of the CTL induced is not demonstrated, let alone in an efficacy tumor model.

The use of proteinD as a fusion partner for E6, E7 and E6E7 fusion is not obvious. The prior art does not suggest either that the increased immunogenicity can be achieved with the combination of such an HPV antigen with a CpG oligonucleotide.

6. In our patent application 09/581976, we describe another, novel, way to induce potent CTL against an early HPV16 antigen, in particular against E7 antigen from HPV16, which is based on the use of a recombinant purified E7 protein produced in *E coli*, fused to helper epitopes provided by a portion of a bacterial protein (PD) and further formulated with CpG

ODN used as adjuvant. Moreover, not only do we demonstrate the effectiveness of the CTL induced in an E7 expressing tumor model, but we also show that in addition to CTL we induced a broader immune response, including CD4 proliferation and although less pronounced, an E7-specific antibody response. These results have been generated with a protein-based approach.

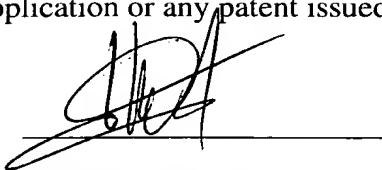
7. The importance of CD4 T cells is now well established in the context of tumor rejection. These cells could either have a direct lytic activity on the tumor, or provide an indirect help to CD8 T cells through the secretion of appropriate cytokines. When an exogenous protein is injected it is generally taken up by antigen presenting cells and presented mainly in the context of MHC class II to CD4 cells. It was not obvious at that time that a vaccine made of a purified protein formulated in an aqueous solution with CpG ODN would lead to the generation of CTL and would lead to tumor rejection. Our data show that it is indeed the case suggesting that the presence of CpG as adjuvant has helped the protein to be delivered into the APC in a different pathway which lead to presentation in Class I HLA and CTL activation.

8. Concomitantly to our experiments, the publication from Chu et al. published in November 97 (J Exp Med 1997 186: 1623-1631: CpG oligodeoxynucleotides act as adjuvants that switch on T helper 1 (Th1) immunity. Chu RS, Targoni OS, Krieg AM, Lehmann PV, Harding CV.) confirmed that CpG could work as an adjuvant that switch on TH1 immunity, this, at least when combined to the Hen Egg Lysozyme (HEL) antigen. It was however not obvious at the time this paper was written and at the time we were conducting our experiments that CpG ODN would work with any other antigen, let alone with a **cancer** antigen.

9. Late antigens from HPV like L1 or L2 are known to form VLP which are immunogenic by themselves and induce antibody responses able to protect against HPV infection.

10. I declare that all statements made herein based on my own knowledge are true and that all statements based on information and belief are believed to be true; and further that the statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United

States Code, and that such willful false statements may jeopardize the validity of the above application or any patent issued therefrom.

A handwritten signature in black ink, appearing to be 'C. Gérard', is written over a horizontal line.

Catherine Gérard, Ph.D.

Date: October 23, 2003